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CURRENT OPINION

View point: what should the future design of clinical imaging studies be?

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The ischaemic cascade

Coronary artery disease (CAD) is primarily a structural disease characterized by the build-up of atherosclerotic plaques in the coronary arteries. With progressive impingement on coronary blood flow, a given coronary stenosis will elicit functional consequences that are described by the 'ischaemic cascade' and emerge progressively as inducible changes of perfusion, wall motion, and electrocardiogram, and finally manifest as chest pain (*Figure 1*). Thus, definitions for clinically significant CAD may vary considerably based on whether rather anatomical vs. functional criteria are used (*Table 1*).

Paradigms of cardiac imaging

Soon after F Mason Sones seminal first angiography on 30 October 1958 in the Cardiac Laboratories of the Cleveland Clinic, the diagnosis of CAD was largely based on angiographical documentation of coronary stenoses. The term 'significant CAD' was defined by the presence of coronary stenoses exceeding a certain threshold of luminal diameter narrowing (50 or 70%).[1] Over the last three decades; however, several non-invasive techniques have been developed, validated, and widely accepted for the diagnosis of CAD. They include stress-echocardiography (stress-echo), single photon emission computed tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance (CMR), and CT coronary angiography (CTCA). Except for CTCA, the majority of non-invasive techniques is aiming at detecting myocardial perfusion abnormalities caused by coronary stenoses, by either assessing the regional distribution of 'contrast agents' throughout the left ventricular myocardium or changes in regional wall motion during conditions of stress or hyperaemia. In the 1990s, fractional flow reserve (FFR) was developed as a way of assessing the functional significance of a given coronary stenosis during invasive angiography using an intracoronary pressure wire. To establish its value as a functional test that would predict myocardial ischaemia, FFR was validated in several studies against the non-invasive functional tests that were more established at that time, predominantly SPECT or stress-echo.

Confused at a higher level

It is one of the most fundamental—albeit unexpected—realities in CAD that the agreement between anatomical (i.e. degree of coronary stenosis) and functional (i.e. myocardial perfusion) aspects is poor.[2–7] In other words, a given diameter narrowing of 60% in a coronary artery may be haemodynamically relevant in patient A, while in patient B the same stenosis is not flow-limiting. The reason for this variability is summarized in *Figure 2* and relates to the fact that myocardial blood flow is determined by many other factors besides diameter stenosis which are poorly appraised by conventional angiography. Hence, a perfect agreement between functional tests of myocardial ischaemia and angiographical gold standards of coronary artery structure is by nature impossible, since different aspects of CAD are visualized. And yet, ironically, the majority of non-invasive tests have been validated against conventional CA claiming the superiority of one or the other modality, if a higher diagnostic accuracy was obtained against the gold standard of invasive angiography.[8–11]

From imaging to clinical impact

In search of an appropriate definition for CAD, one should consider those nosological features that will have an impact on the patient's prognosis and therefore guide treatment. Several large-scale follow-up studies have demonstrated that myocardial ischaemia as detected by non-invasive functional testing is one of the strongest predictors of outcome in stable CAD patients, regardless of whether it is caused by a 50% or a 70% coronary artery stenosis.[12–14] Accordingly, the concept of ischaemia-guided coronary revascularization has emerged.[15,16] The FAME I trial has strengthened this concept by demonstrating that an ischaemia (FFR)-guided revascularization strategy improves patients' outcomes compared with an angiography-guided strategy.[17] Finally, the FAME II trial has proved—for the first time in a prospective randomized setting—the superiority of revascularization over optimal medical treatment for patients with flow-limiting coronary stenoses (FFR <0.80).[18] Accordingly, the definition of clinically relevant CAD has shifted from significant stenoses

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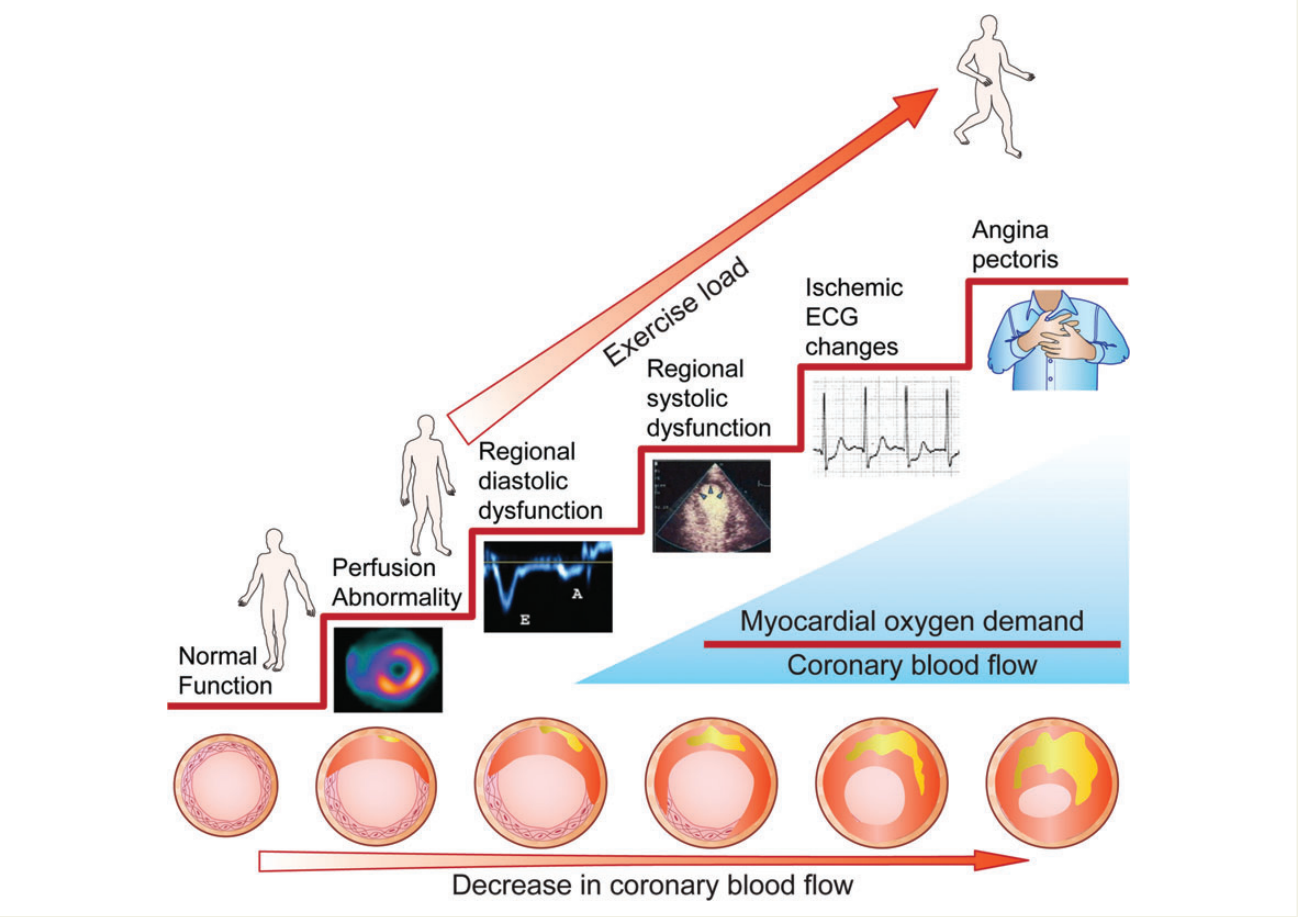

Figure 1 The ischaemic cascade: this concept assumes that with an increasing mismatch between coronary blood flow and myocardial oxygen demand, coronary stenoses will elicit functional consequences in the supplied myocardium, i.e. changes of perfusion, diastolic or systolic wall motion, electrocardiogram, and finally manifest as chest pain.

Table 1 Semantics of coronary artery disease and optimal diagnostic testing

Definition of CAD	Optimal diagnostic test
Endothelial or microvascular dysfunction	Absolute flow quantification with PET, physiological ICA studies (e.g. acetylcholine)
(Epicardial) coronary atherosclerosis	CTCA, ICA (with or without intravascular imaging, i.e. IVUS, OCT)
Ischaemic heart disease	SPECT, PET, S-Echo, perfusion CMR, ICA with FFR

CAD, coronary artery disease; PET, positron emission tomography; ICA, invasive coronary angiography; CTCA, CT coronary angiography; IVUS, intravascular ultrasound; OCT, optical coherence tomography; SPECT, single photon emission computed tomography; S-Echo, stress-echocardiography; CMR, cardiac magnetic resonance; FFR, fractional flow reserve.

(defined as % luminal narrowing) to haemodynamically relevant stenosis (as reflected by ischaemia on non-invasive imaging or a reduction in the FFR value at angiography).

Coronary arteries and the microcirculation

However, several areas of uncertainty remain: It is still unclear how FFR compares with functional imaging techniques and some have suggested considerable disagreement.[19,20] Fractional flow reserve does not account for alterations of microvascular or endothelial vasoreactivity which may contribute to myocardial ischaemia under certain conditions and influence prognosis (*Table 1*).[21,22] For instance, in the presence of severe microvascular dysfunction, FFR values across a given coronary stenosis following adenosine-induced hyperaemia may be blunted. This could result in an underestimation of pathophysiological severity of epicardial coronary disease, while at the same time myocardial blood flow could be markedly reduced thereby contributing to myocardial ischaemia and impaired prognosis (*Figure 3*).[22] Conversely, relatively healthy subjects with marked hyperaemic microvascular vasodilation may exhibit borderline FFR values slightly <0.80 across a given stenosis, despite preserved hyperaemic myocardial blood flow. This is why early validation studies of FFR performed in relatively 'healthy' subjects with predominantly one-vessel disease found the ideal cut-off for predicting

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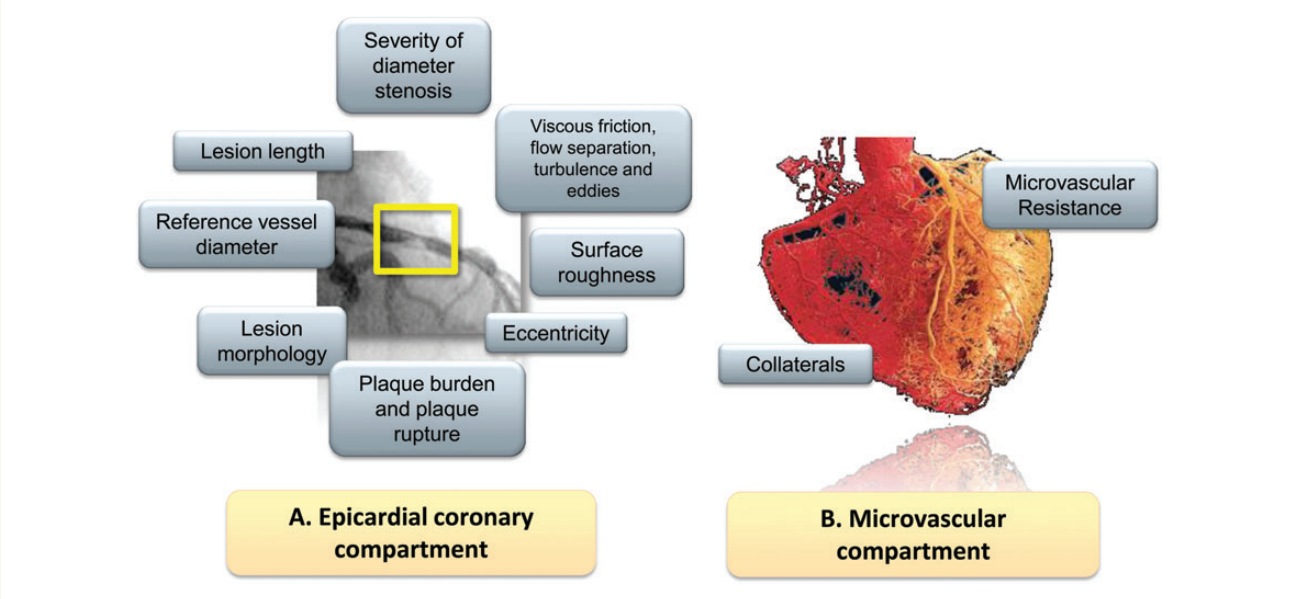

Figure 2 Myocardial blood flow is determined by a variety of factors that affect the epicardial coronary compartment (*A*) or the microvascular compartment (*B*). The epicardial coronary compartment is generally affected by coronary atherosclerosis obstructing conductive blood flow (*A*). However, besides the angiographical severity of diameter narrowing, several other factors that are not or only poorly captured by invasive angiography can modulate the haemodynamic relevance of a given lesion. (*B*) However, under resting conditions, 90% of coronary vascular resistance resides in the microcirculation (arterioles and pre-arterioles). Microvascular dilation in response to various stressors is crucial to match blood flow with myocardial oxygen demands. This regulation of microvascular resistance can be disturbed in the presence of a variety of functional or structural pathologies and thereby contribute to myocardial ischaemia.

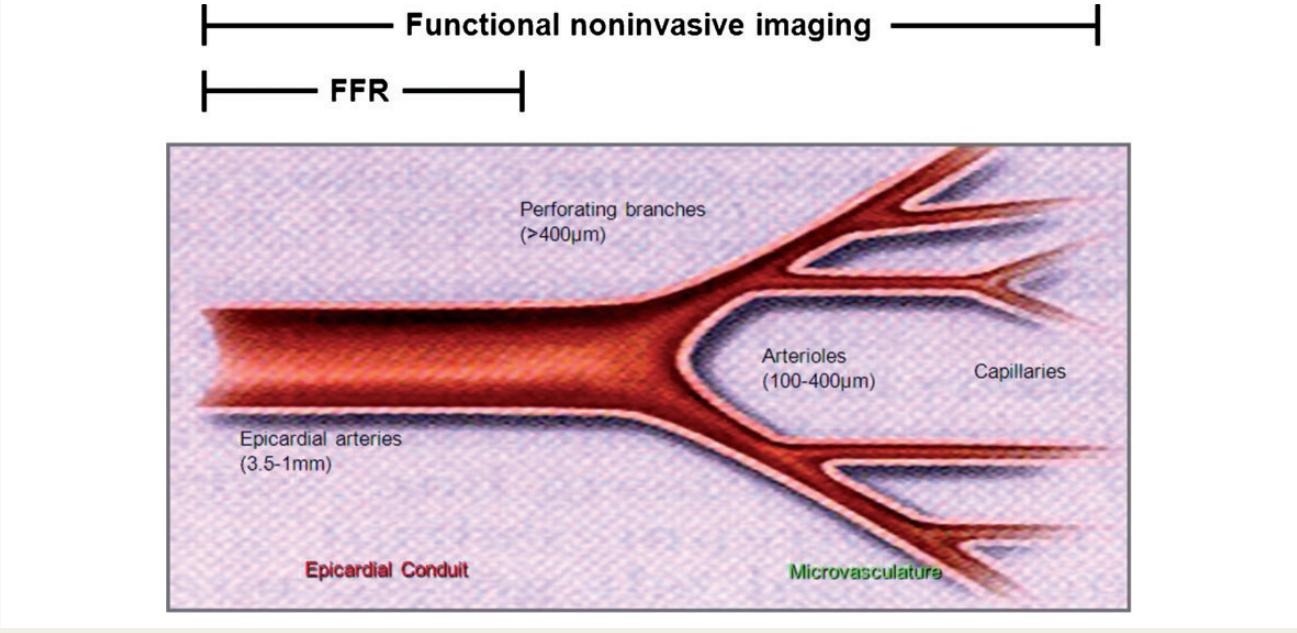

Figure 3 Comparison of fractional flow reserve vs. Non-invasive imaging modalities. Fractional flow reserve assesses only the pressure gradient across a lesion in the epicardial coronary arteries. However, ischaemia by myocardial perfusion imaging is an integrated measurement of blood flow through the epicardial and microvascular compartement and, therefore, can also be affected by microvascular or endothelial dysfunction.

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myocardial ischaemia to be in the range of 0.72–0.75, i.e. considerably lower than the currently accepted cut-off of 0.80.[20]

From pictures to outcome

All of the above have important implications for the design of future imaging studies: at present, there is considerable discussion which of the available imaging techniques is most accurate to diagnose CAD, and a number of comparisons using CA as the gold standard have been conducted and employed to prove the superiority of one technique over the other. However, given the changing paradigm of CAD, this approach appears outdated. Additionally, one should also realize that perfusion and systolic function as markers of ischaemia may represent different phenomena and may therefore not be directly comparable. Consequently, trials are needed that are designed to demonstrate that non-invasive imaging can guide treatment and subsequently improve patients' outcome. Such trials may follow the design of the FAME I and II trials and thereby continue the exemplary path that FFR has set in invasive cardiology.[17,18] Accordingly, efforts across countries are currently joined to design appropriately sized prospective randomized trials to test this hypothesis.[23] In an era of ever increasing pressure from financial reimbursement systems such trials are eagerly needed to solidify the role of non-invasive cardiac imaging in cardiology. By these means, clinical validation of established or novel cardiac imaging techniques will centre around the ultimate and most important gold standard in cardiology: guidance of therapy aiming at improvement of patients' outcome.

Conflict of interest: none declared.

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